

1 **Chronic lymphocytic leukaemia (CLL)/small-cell lymphocytic lymphoma (SLL) of the lacrimal sac: a**
2 **case series**

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22 Conflicts of Interest: None.

23 Source of Funding: None.

24 **Running Title:** Chronic lymphocytic leukaemia of the lacrimal sac.

25 **Abstract**

26 Background: Lymphomas of the lacrimal sac are rare accounting for less than 10% of lacrimal sac malignant
27 tumours. They may present with symptoms typical of secondary acquired nasolacrimal duct obstruction and
28 are thus often misdiagnosed.

29

30 Methods: Case series and literature review.

31

32 Results: Herein we describe 3 cases of chronic lymphocytic leukaemia (CLL)/small-cell lymphocytic
33 lymphoma (SLL) of the lacrimal sac with immunohistochemical and in 1 case molecular confirmation.

34

35 Conclusion: Lymphomas of the lacrimal sac should be suspected in patients with known CLL presenting
36 with epiphora and dacryocystitis. During dacryocystorhinostomy (DCR), an incisional biopsy of the lacrimal
37 sac is essential for confirming CLL/SLL involvement and may guide treatment.

38

39 Key Words: Lacrimal sac, lymphoma, chronic lymphocytic leukaemia, dacryocystitis, epiphora.

40 Malignant tumours of the lacrimal sac are uncommon with close to 90% of these being of epithelial origin.
41 Lymphomas of the lacrimal sac are rare [1-3]. They may present with symptoms typical of secondary
42 acquired nasolacrimal obstruction including epiphora with a medial canthal mass and thus often
43 misdiagnosed. It should be suspected in patients with known CLL presenting with epiphora and
44 dacryocystitis. During DCR an incisional biopsy of the lacrimal sac is essential for confirming CLL/SLL
45 involvement and may therefore guide adjuvant treatment [1-7].

46
47 All patients had signed a written informed consent form and the study was conducted in accordance with the
48 declaration of the Declaration of Helsinki.

49 **Case Reports**

50
51 Case 1: An 89 year-old male, with past medical history of CLL and left external DCR, presented to the eye
52 department with a painful, discharging, cystic swelling in the right lacrimal sac area. He was treated with
53 antibiotics for his right-sided dacryocystitis, and later listed for a right external DCR. Perioperatively, the
54 lacrimal sac was noted to be inflamed, and hence an incisional biopsy taken.

55
56 The specimen extended 8x5x3mm. Histological examination revealed: a diffuse atypical lymphocytic
57 infiltrate with mild nodularity; intermediate-sized cells with coarse nucleus and prominent nucleoli and large
58 cells with prominent nucleoli in proliferation centres (Fig. 1A&B). Ki67 immunostaining showed a
59 moderate growth fraction with mitotic cells localized in proliferation centres (Fig. 1C). Further evaluation
60 with immunohistochemistry (IHC) confirmed monotypic B cells with positive staining for: CD5; CD20;
61 CD23; CD79a; (Fig. 1D-F) BCL-2 with synthesis of IgM, IgD and equivalent staining of kappa and lambda
62 light-chains, with a moderate background scattering of CD3+ T-cells. The following immunostains were
63 negative: cyclin-D1, CD21, CD10 and BCL-6. Histological and IHC features were consistent with diffuse,
64 well-differentiated CLL/SLL. Immunoglobulin heavy-chain polymerase chain reaction (IgH-PCR)
65 demonstrated a monoclonal B-cell population. Furthermore, next generation sequencing was performed as
66 previously described [8]. Briefly, target exons of 15 selected genes relevant to CLL were sequenced using
67 Ion Torrent Personal Genome Machine (PGM) and Torrent Suite Pipeline v4 (Life Technologies, UK).
68 Genes included were: *TP53* (exons 2-11) and *SF3B1* (exons 8-20); *ATM* (exons 2-63); *MYD88* (exons 2-5);

69 *BIRC3* (exons 2-9); *NOTCH1* (exon 34); *XPO1* (exons 11-16); *LRP1B* (exons 34-86); *FBXW7* (exons 5-12);
70 *HIST1H1E* (exon 1); *ZFPM2* (exon 8); *SAMHD1* (exons 1-16); *CHD2* (exons 12-36); *POT1* (exons 5-19)
71 and *PCLO* (exons 2-24). This molecular panel has previously been reported to be associated with extensive
72 nodal involvement indicating advanced stages of CLL and thus relevant for its prognosis [8]. Next
73 generation sequencing was performed in this case to ascertain whether or not lacrimal sac involvement is
74 associated with any of these gene mutations. No somatic gene mutations were detected in the sample.

75
76 The patient was already under the care of haematologists and had received chemotherapy – previous course
77 of chlorambucil followed by bendamustine. He was given a further single lower dose of bendamustine. His
78 lacrimal stents were removed 6 months post successful DCR and he was given a further 6 month follow up
79 appointment. Prior to his appointment at the eye department, the patient had surgery for a sebaceous cell
80 carcinoma on his calf involving excision and grafting, which unfortunately failed and found to be infected
81 with *Pseudomonas*. He subsequently developed sepsis and was treated with intravenous antibiotics but
82 rapidly deteriorated, and died within 4 days of admission.

83
84 Case 2: A 66 year-old male, with known CLL in the past, presented with a 6 month history of epiphora and a
85 painless hard mass over the right lacrimal sac. Computed tomography revealed a soft tissue mass, measuring
86 approximately 20x22x16mm, in the medial canthal region extending into the lacrimal fossa and nasolacrimal
87 duct into the nasal cavity. A right external DCR with an incisional biopsy of the lacrimal sac was performed.

88
89 Histopathological analysis showed: a nodular and diffuse infiltration by intermediate-sized, round
90 lymphocytes punctuated by pale-staining proliferation centres containing pro-lymphocytes and para-
91 immunoblasts. There was an unusual degree of stromal fibrosis, marked perineural and perivascular
92 sclerosis. Tumour cells had a classical CLL phenotype: CD5+; CD20+; CD21+; CD23+; CD79a+; MUM-
93 1+ and BCL-2+ with synthesis of IgM. CD3, CD10, cyclin-D1 and BCL-6 stains were negative. The Ki-67
94 growth fraction was <5%. Plasma cells within sclerotic areas showed indeterminate light-chain staining.
95 Overall, features were consistent with lacrimal sac involvement by SLL/CLL.

96

97 The patient had low-dose local radiation of the lacrimal sac area alone, as further disease was not detected
98 elsewhere on staging. The patient was re-referred to the eye department 2 years later for persistent epiphora
99 secondary to post irradiation scarring. There was a complete response locally but the patient suffered a
100 relapse of the CLL elsewhere, received further chemotherapy, and was subsequently lost to follow up at the
101 eye department.

102

103 Case 3: A 75 year-old female, with a past medical history of: CLL (p53 deletion) treated with fludarabine
104 and cyclophosphamide; successful left external DCR for recurrent dacryocystitis but local drainage of the
105 right lacrimal sac due to relapse of her CLL, presented with a recent 6-month history of intermittent right eye
106 epiphora. Clinically there was right nasolacrimal duct obstruction but no palpable mass. During external
107 DCR, the right nasal process of frontal bone was noted to have a soft consistency with a spongy mucoid
108 appearance and therefore prompted a biopsy. There was no obvious tumour noted in the lacrimal sac.

109

110 Histological assessment was limited due to a very small specimen and marked traction artefact. Of note,
111 however, small fragments of trabecular bone showed dense infiltration of the intratrabecular stroma by
112 lymphoma (Fig 2A&B). The tumour comprised small lymphocytes with scanty pale cytoplasm and small,
113 round nuclei with condensed chromatin and no nucleoli. The cell infiltrate were CD20+, CD79a+, CD5+,
114 CD23+ (Fig 2C-E), BCL-2+, IgM+, IgD+ with kappa light-chain restriction; but negative for CD10, p53,
115 MUM-1, CD43 and cyclin D1. The Ki-67 growth fraction was <5%. There was marked reduction of CD3+
116 and CD5+ reactive T-cells. Histological and IHC appearances were consistent with involvement by
117 SLL/CLL.

118

119 The patient was referred back to haematologists and treated with chlorambucil and ofatumumab. She has
120 been in remission for 5 years.

121

122 Discussion

123 Lymphomatous involvement of lacrimal sac may be primary or secondary. There are <70 primary cases and
124 few case reports/series of secondary involvement. Previous reporting would have been variable due to lack
125 of global consensus regarding lymphoma classifications until the Revised European-American Classification

126 of Lymphoid Neoplasms, the WHO classification, and later the EORTC ophthalmic oncology task force
127 study defining the clinical and histopathological characteristics [1-3, 9-10]. From the EORTC study of 15
128 primary lacrimal sac lymphoma cases, 33% of cases were classified as diffuse large B cell lymphoma
129 (DLBCL; non-Hodgkin's lymphoma), 33% as extranodal marginal zone B cell lymphoma of mucosa
130 associated lymphoid tissue (MALT lymphoma), 20% were classified as transitional MALT lymphoma with
131 features between MALT lymphoma and DLBCL, and 13% as unclassified B cell lymphomas [10]. Of the
132 other in the literature, it appears that DLBCL and MALT lymphomas occur with approximately equal
133 frequency [1-3, 5, 7, 9-11]. However, DLBCL has been more frequently described in association with
134 systemic lymphoma [2-3, 7].

135

136 Lymphomas account for ~2-6% of lacrimal sac malignant tumours, present in generally older patients with
137 symptoms typical of secondary acquired nasolacrimal obstruction including epiphora, medial canthal mass;
138 thus often misdiagnosed as acute or chronic dacryocystitis [4-7]. It should be suspected in patients with
139 known CLL presenting with epiphora and dacryocystitis. DCR with stenting is well-tolerated and effective
140 at alleviating symptoms. During DCR an incisional biopsy of the lacrimal sac is essential for confirming
141 CLL/SLL involvement, even in the absence of obvious swelling (as in 1 of our cases), and may guide
142 adjuvant chemo- and/or radiotherapy treatment [1-4, 6]. Treatment is usually a combination of surgery,
143 irradiation and /or chemotherapy (notably regimens involving chlorambucil) but no commonly agreed
144 treatment regimen for periocular lymphoma exists because of the limited number of patients seen [2-3, 7, 10-
145 11].

146

147 In keeping with earlier reports [2-3], our patients had systemic CLL with secondary lacrimal sac infiltration,
148 were elderly but one had presumed bilateral involvement (2 DCRs) and one with bony destruction which are
149 rare. Two of the patients had been treated with chemotherapy (including chlorambucil) whilst one had low-
150 dose local area irradiation as no further disease was detected.

151

152 In summary, CLL/SLL infiltration of the lacrimal sac is rare and should be suspected in any patient with
153 systemic CLL presenting with epiphora and/or lacrimal sac area mass. Herein we present 3 cases with
154 immunohistochemical confirmation and one where molecular testing was available – which, to our

155 knowledge, has not been previously reported. However, we do recognize that no somatic mutations were
156 detected even though this molecular panel has previously been reported to be relevant for CLL prognosis and
157 treatment response [8]. Whether or not lacrimal sac involvement is associated with the same somatic gene
158 mutations requires further evaluation.

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